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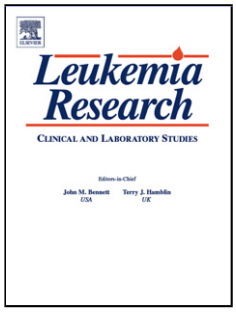

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Leukemic transformation and second cancers in 3649 patients with high-risk essential thrombocythemia in the EXELS study

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Highlights

- Essential thrombocythemia (ET) has a risk of malignant transformation
- We determined transformation to acute myelogenous leukemia (AML)
- Standardized incidence ratio of AML was high in ET patients on hydroxycarbamide
- No cases of AML occurred in ET patients treated with anagrelide
- Rates for non-AML cancers were similar in the two groups

Abstract

EXELS, a post-marketing observational study, is the largest prospective study of high-risk essential thrombocythemia (ET) patients, with an observation time of 5 years. EXELS found higher event rates of acute leukemia transformation in patients treated with hydroxycarbamide (HC). In the current analysis, we report age-adjusted rates of malignant transformation from 3460 EXELS patients exposed to HC, anagrelide (ANA), or both. At registration, 481 patients had ANA treatment without HC exposure, 2305 had HC without ANA exposure, and 674 had been exposed to both. Standard incidence ratios (SIRs) were calculated using data from the Cancer Incidence in Five Continents database to account for differences in age-, gender-, and country-specific background rates. SIRs for acute myelogenous leukemia (AML) were high in ET patients. SIRs for AML were high in HC-treated patients, but AML was rare in ANA-treated patients; no cases of AML were found in patients only treated with ANA. No statistically significant difference was seen between SIRs for ANA and HC treatment for AML or skin cancer. SIRs for other cancers were similar in the HC and ANA groups and close to 1, indicating little difference in risk. Although

statistically inconclusive, this study strengthens concerns regarding possible leukemogenic risk with HC treatment. (NCT00202644)

Key words: acute myelogenous leukemia, malignant transformation, anagrelide, hydroxycarbamide

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Contributions

The study was designed by the international EXELS steering committee (G.B., J.-J.K., C.B., M.G., L.G., C.N.H.), chaired by G.B., who is also the lead and corresponding author, and developed the final draft of the manuscript. Y.F., H.G., and L.H. at the Regional Cancer Centre in Uppsala performed the statistical analyses and interpretation. C.B., M.G., L.G., C.N.H., J.-J.K. all enrolled patients in the study,

analyzed the data, and critically reviewed the manuscript. H.A. contributed to the study management, interpretation of the data, and critically reviewed the manuscript. J.W. provided the data from the EXELS database and critically reviewed the manuscript for data accuracy. All authors provided final approval of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

C.N.H. received honoraria for speaking and advisory board membership from Shire, Novartis, Sanofi, Gilead, Celgene, and CTI Biopharma, and research funding from Novartis. GB received funding for consultancy and honoraria from Shire and Vifor, and Uppsala University received research funding from Shire. J-J.K. received a grant from Shire and grants and personal fees from Novartis. J.W. is an employee of Shire. L.G. received personal fees from Shire. H.A. is an employee of Shire. C.B., F.F., H.G., M.G. and L.H. declare no conflict of interest.

1. Introduction

Essential thrombocythemia (ET) is the most “benign” of the myeloproliferative neoplasms (MPNs), with a near-normal expected life span [1,2]. The median age at diagnosis is approximately 60 years, but a substantial proportion of patients with ET are younger than 60 years at diagnosis. Furthermore, the life expectancy in the general population has progressively improved and reached a point where individuals aged 65 years have an average life expectancy of around 20 years in developed

countries. Therefore risks or side effects associated with ET treatments are especially pertinent.

The main goal of treatment in ET is to prevent thrombosis and bleeding, which represent the most common complications of ET. Risk stratification traditionally includes age > 60 years, previous thrombohemorrhagic events, and platelet counts > $1500x10^9$/L. Patients having any of these risk factors are considered high risk, and all others are considered low risk [3].

First-line cytoreductive therapy in ET in most countries is hydroxycarbamide (HC), especially in older patients [4]. Anagrelide (ANA; Xagrid®), a selective platelet-reducing agent is an alternative therapy, registered as a second-line therapy for ET in Europe; however, ANA is often used as first-line therapy in younger patients due to the concern for a possible leukemogenic risk connected to HC [4]. In the United States, ANA is registered for treatment of thrombocythemia in MPNs, and in some countries, (i.e., Austria, Japan) as first-line therapy for ET.

The Evaluation of Xagrid Efficacy and Long-term Safety (EXELS) study is the largest prospective study ever performed in patients with high-risk ET; it has a follow-up of 5 years from registration, and information on treatment received from diagnosis [5]. More than 90% of the patients were treated with either ANA or HC; hence, the study offers a unique and important opportunity to investigate the effect of these drugs on the event rate of acute leukemia and myelodysplastic syndrome (MDS), as well as on the development of non-hematological malignancies. The thrombohemorrhagic complications and risk factors have been previously published [5]. This study identifies concerns regarding the risk for acute leukemia and second malignancies as a function of treatment.

2. Subjects and methods

2.1 Patients

The EXELS study was a prospective, 5-year, observational study recruiting 3649 high-risk ET patients from 125 centers in 13 European countries between 2005 and 2009, with an observation time of 5 years (NCT00202644). The main objectives of the study were safety and pregnancy [5].

The EXELS study was initiated in 2005 and finished in June 2014. All centers obtained local ethical approval prior to patient enrollment. Patients were eligible for study enrollment if they had a known date of birth; confirmed diagnosis of ET; and the presence of 1 or more high-risk features at the date of screening, according to the treating physician: age > 60 years, a history of thrombohemorrhagic events, or initial platelet count > $1000x10^9$/L (the accepted platelet high-risk criterion when the study was initiated). At the time of study initiation, either Polycythemia Vera Study Group (PVSG) (10) or World Health Organization (WHO) 2001 or 2008 (11) diagnostic criteria may have been used; no particular one was mandated. When the study was initiated in 2005, no recurrent mutations had been identified in ET, thus such data were not prospectively collected. For inclusion in the study, patients were required to be either already prescribed cytoreductive therapy or in need of treatment at the time of study registration. Treatment was given at the discretion of the investigators. The majority (95%) of patients had previous treatment; 5% were treatment-naïve at registration. Previous cytoreductive treatment was recorded at registration, and changes in treatment were recorded during follow-up. Data were collected using an electronic data capture system at registration, every 6 months, and upon pre-defined

events such as thrombohemorrhagic events, transformation, non-hematologic malignancies, serious adverse events, or death. Two patients were excluded from the study because of an unknown date of birth. Thus, 3647 participants from the EXELS study were included in the cohort investigated in this study. Baseline study enrollment characteristics are shown in Table 1. Results on thrombosis, hemorrhage, and safety have been published previously [5]. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

2.2 Statistical analysis

Exposure to ANA and HC was recorded at study enrollment, based on recorded patient history. Only patients ever treated with HC or ANA alone or in combination were included in the current analysis. Transitions between different treatment groups were allowed during follow-up. All patients were followed until death or until end of study. The duration of exposure was calculated from the treatment history before enrollment and observation during study follow-up. Relative risks were only estimated for events occurring within the observed study period, from the registration date to the end of follow-up. One hundred eleven patients switched from ANA to HC, and 291 patients switched from HC to ANA during the study. For a patient to be categorized in one of the treatment groups, we required a minimum exposure time of at least 180 days. The overall risk for hematological transformation or non-hematological malignancy after study enrollment was studied by estimating the cumulative incidence, treating death from other causes as a competing risk. To compare treatments with regard to transformations and non-hematologic malignancies, we used standardized incidence ratios (SIRs) standardized on age,

gender, and country of residence. Background incidence rates were retrieved from the Cancer Incidence in Five Continents (CI5) database [http://ci5.iarc.fr]. Age during follow-up was split into 5-year categories (15–19, 20–24, etc.). Byar's Poisson approximation was used to estimate 95% confidence intervals (CIs). In the case of no events, the SIR was zero and CIs were calculated accordingly. Relative risks for HC versus ANA were calculated as ratios of SIRs [6]. Bias-corrected accelerated bootstrap with 10000 samples was used to estimate 95% CIs around these risk ratios [7]. All data management was done with SAS version 9.4 (SAS Institute, Cary, NC, USA), and all statistical analysis was performed in R version 3.2.1. (*R* Foundation for Statistical Computing, *Vienna*, Austria). Country incidence rates for MDS could not be found in the CI5 database, and therefore, MDS was not included in this analysis.

A sensitivity analysis was performed on the subset of patients with information on the date of ET diagnosis. Further sensitivity analyses included only incident cases (ET diagnosis within 1 year of registration). Analyses were stratified by time between ET diagnosis and registration. To investigate early and late risks, follow-up time was split into different durations of exposure.

3. Results

A total of 3460 patients were exposed to HC, ANA, or both at registration. Disease duration was long. Thirteen per cent of the patients were diagnosed with ET >10 years before registration, and only 23 % received their ET diagnosis within a year before registration. Patients were categorized according to treatment exposure at registration as follows: 481 patients had ANA treatment at registration and had not been exposed to HC, 2305 had HC and had not been exposed to ANA, and 674

patients were exposed to both drugs (Fig. 1). Five hundred forty patients switched from HC to ANA, and 116 switched from ANA to HC before registration. The medication distribution by age group was as follows: < 40 years (n = 249): ANA 41%, HC 21%, ANA+HC 24%; 40–59.9 years (n = 931): ANA 26%, HC 41%, ANA+HC 26%; 60–79.9 years (n = 1994): ANA 6%, HC 75%, ANA+HC 15%; 80+ years (n = 473): ANA 3%, HC 81%, ANA+HC 11%. Median age was 51 years in the ANA group and 71 years in the HC group.

3.1 Non-hematologic malignancies

One hundred seventy-four cases of non-hematologic cancer, including 35 cases of skin cancer, were recorded (Table 2). The SIRs for all malignancies were close to 1 for all treatment groups (Table 3), indicating similar risks as in the background population. For all skin cancers, including melanoma, the SIR for patients who received HC treatment was higher than expected and higher than for patients who received ANA (1.15 versus 0.45, respectively). When melanoma was excluded, the figures changed only marginally (Table 3). However, possibly due to the low number of events, the CIs were wide, and no statistically significant difference was found between treatments (Table 3).

3.2 Acute leukemia/ myelodysplastic syndrome

All observed cases of acute leukemia were myelogenous (AML). AML emerged at approximately the same rate during the 5 years of observation.

Sixty-seven cases of AML and 19 cases of MDS were recorded (Table 2). The SIRs for AML were markedly elevated for all treatment groups except ANA, indicating

a much higher risk for AML in patients with ET compared with the background population (Table 3). Overall, 39 of 67 AML cases were found in the HC group (8970 person-years of treatment, SIR 39.7). Baseline characteristics of these patients are presented in Supplemental Table 1. Another 20 AML patients were found in the group that switched from HC to ANA (2934 person-years of treatment, SIR 91.5), Table 3. No cases of AML were found in the ANA-only group (1905 person-years of treatment, SIR 0), and only 3 cases were found in the group switching from ANA to HC during the study (Table 3). As the number of AML cases in the ANA-only group was 0, no statistical expression can be calculated for the difference to the HC group.

For patients who changed therapy, the risk ratio for developing AML for patients who switched from HC was more than doubled (2.30–2.52), irrespective of minimal exposure time (Table 4). A calculation of risk ratio for patients who switched from ANA to HC, based on the only 3 AML cases in this group, is more uncertain, but also showed an increased risk ratio (1.72–1.70; Table 4). As mentioned previously, there are no background data for MDS in the CI5 database. In a separate analysis, the MDS cases were added to the AML cases, using the AML background SIR, but this did not change the results (data not shown). Two patients in the HC group who developed AML had previous treatment with busulphan, 4 with pipobroman.

The rate of AML occurrence did not change over the time of the study, nor was there an increased rate of leukemia with increasing time from diagnosis.

4. Discussion

These data from the EXELS study offer an opportunity to compare malignant transformation for the 2 main treatments used in high-risk ET. Higher event rates for non-hematologic malignancies were previously shown in this cohort. We have also

previously shown that the event rate for AML per 100 years of exposure in the EXELS study was lower in the ANA group compared with other cytoreductive treatment (0.07 versus 0.28 per 100 years exposure, respectively) and transformation to MDS only occurred in the HC group (event rate 0.12 per 100 years exposure) [5]. However, these data are difficult to interpret with certainty due to the difference between the age of patients receiving HC and ANA and the known influence of age on the incidence of malignancies. Because treatment was given at the discretion of the treating physician, there is a possible bias if HC was given in cases that the physicians considered more aggressive. The influence of the age difference between the ANA and HC group in the present analysis was handled by the use of SIRs. Importantly, the difference between the treatment groups persisted in the SIR analysis.

We found that not only did patients with ET in the EXELS study have a substantially increased risk for AML development, but there was also a highly skewed distribution of AML cases between the HC and ANA treatment groups. Interestingly, no patient in the ANA-only group developed AML during 1905 person-years of ANA treatment (SIR 0.0), whereas 39 patients in the HC group did so during the 8970 person-years of HC treatment. Compared with the background population, the SIR for AML was 40-fold higher than expected under HC exposure. The SIR for patients who switched from HC to ANA was even higher, approximately 90-fold, with an observed number of 20 versus an expected of 0.22 during 2934 person-years. The fact that two of the AML patients in the HC group had previous treatment with busulphan and four with pipobroman, gives support to previous reports on leukaemia risk with combination of HC and other chremotherapy.

Acute leukemia is a complication of ET and occurs even in the absence of treatment [8], making it difficult to conclude whether or not a certain drug is leukemogenic. Two previous studies comparing HC and ANA treatment, the ANAHYDRET study [9] and the PT1 study [10], have reported leukemia rates. In the ANAHYDRET study no cases of leukemia transformation were found; in the PT1 study there were 10, 6 vs 4 for HC and ANA, respectively, but no further statistical analysis was made. It is generally accepted that busulfan, P32, pipobroman, and a combination of any cytostatic drugs increase the risk for leukemia transformation [11]. With regard to HC, the standard first-line therapy for ET in most countries, the published data are conflicting [11,12], and there is no consensus about how to interpret the evidence [13–15]. However, concern about potential leukemogenicity of HC therapy influences treatment choice, as well as published guidelines. “Caution” with HC in younger patients is advocated in the European LeukemiaNet (ELN) recommendations [3]. HC is second-line therapy in younger patients in guidelines in many countries, and studies on treatment choice in Europe show that a minority of patients aged < 40 years receive HC treatment. Instead, ANA is mostly used as first-line therapy in younger patients, also previously demonstrated from the EXELS data [4]. Notably, the high SIR for AML in patients who switched from HC to ANA may be interpreted as a higher risk for patients resistant to HC, in line with the findings of Alvarez-Larran *et al*. in patients with polycythemia vera [16]. Alternatively, it could be interpreted as a higher risk for patients exposed to both drugs, which seems less likely, because ANA has no mutagenic properties, and we observed no cases of AML in patients exclusively treated with ANA.

Patients with ET have a long expected survival. Even when diagnosis is made at around 65 years of age, high-risk patients will get cytoreductive therapy for

decades. These facts make the risk–benefit balance of treatment particularly sensitive. Therefore, minimizing the risk of treatment damage is one of the central goals of management [3], especially vis-à-vis life-threatening complications like transformation to acute leukemia. This is the reason why cytostatic drugs with known or suspected leukemogenicity are avoided in younger patients (sometimes defined as < 40 years of age, sometimes < 60 years) with a long expected treatment duration. In our view, the data we present here strengthen concerns regarding a possible leukemogenic effect of HC. The lack of statistically significant differences between HC- and ANA-treated patients and the development of AML may either be due to a true lack of difference or that this very large study lacks the power to demonstrate a difference.

The rate of AML occurrence did not change over time. This may, however, be an artefact, as the patients were included in this study at varying times from diagnosis, but the complication of acute leukemia was studied only after registration. This means that patients with ET who had developed AML after diagnosis and before the start of the study could not be included in the study. This, in turn, infers a risk for “immortal time bias”: the patients included may be long-term survivors compared with other patients with ET, and patients prone to develop AML early may be under-represented in the study.

For skin cancer, the SIR for HC-treated patients was slightly higher than in a normal population and higher than in the ANA group. In spite of these trends, there was no statistically significant difference between HC and ANA groups. Nonetheless we continue to recommend scrutiny for the development of skin cancer in patients with receiving treatment.

A wide range of other cancers were recorded, with no other group being as large as skin cancer. For these malignancies the SIRs were close to 1, indicating no increased risk for any treatment group. This is another important finding because the prevalence of cancer survivors is high and concerns that ET treatments might influence either the development or relapse of such cancers could impact treatment decisions. However, other smaller studies have shown conflicting results [17,18].

The current study adds to the evidence that the risk for AML is strongly increased in patients with ET compared with a normal population. In EXELS, there was also a consistent numerical difference in the incidence of AML between patients receiving HC versus ANA treatment, even if the difference did not reach statistical significance. The study thus strengthens concern for a possible leukemogenic effect of HC, and the caution advocated by the ELN consensus treatment recommendations [3] seems well advised.

Furthermore, patients switching therapy, particularly from HC to ANA, had a significantly increased SIR for AML compared with those who received HC, suggesting that patients needing to switch therapy are at increased risk. Skin cancer was also more common in HC-treated patients and showed an SIR slightly higher than a normal population, but was not statistically significantly different from ANA-treated patients. Even during a substantial person-year experience and a follow-up of 5 years, no new concerns emerged related to ET or to either drug regarding other non-hematological malignancies.

Contributions

The study was designed by the international EXELS steering committee (G.B., J.-J.K., C.B., M.G., L.G., C.N.H.), chaired by G.B., who is also the lead and corresponding author, and developed the final draft of the manuscript. Y.F., H.G., and L.H. at the Regional Cancer Centre in Uppsala performed the statistical analyses and interpretation. C.B., M.G., L.G., C.N.H., J.-J.K. all enrolled patients in the study, analyzed the data, and critically reviewed the manuscript. H.A. contributed to the study management, interpretation of the data, and critically reviewed the manuscript. J.W. provided the data from the EXELS database and critically reviewed the manuscript for data accuracy. All authors provided final approval of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

C.N.H. received personal fees from Novartis, Celgene, CTI Biopharma, Gilead, Roche, and AOP Pharma, and research funding from Novartis. G.B. received personal fees from Vifor, and research funding and writing support from Shire. J-J.K. received personal fees from Novartis, and research funding from Novartis and Shire. L.G. received personal fees from Shire. H.A. and J.W. are employees of Shire. C.B., F.F., H.G., M.G. and L.H. declare no conflict of interest.

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an Ashfield Company, part of UDG Healthcare plc, and supported by Shire International GmbH. Although the sponsor was involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication was made by the authors.

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Fig. 1. Distribution of Patients Exposed to ANA and HC in the EXELS Study.

Two patients of those initially registered were excluded because of unknown date of birth. *Dates were missing In 18 patients exposed to both drugs.

FIGURE FILE UPLOADED SEPARATELY

Abbreviations: ANA = anagrelide, HC = hydroxycarbamide

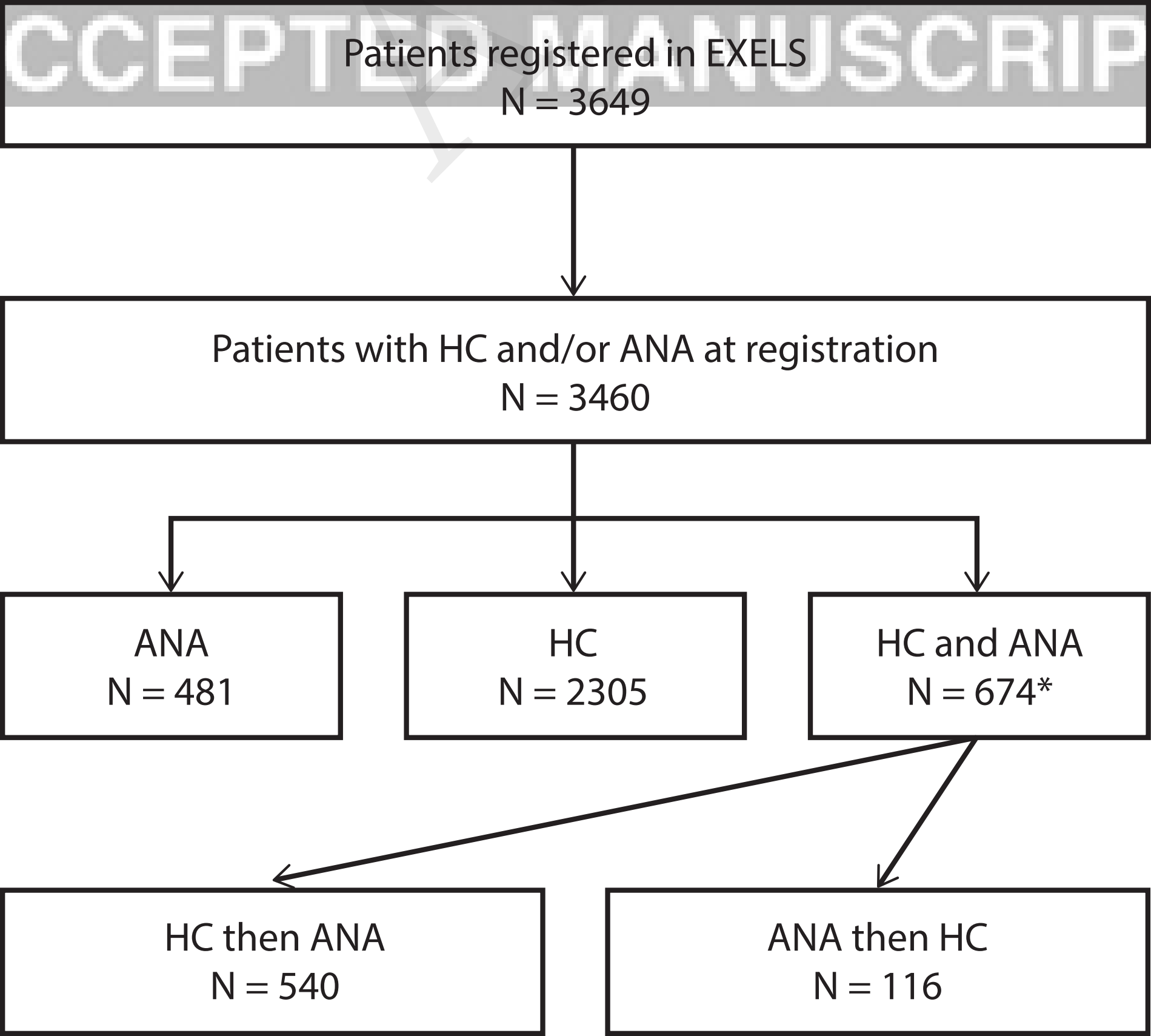

Table 1

Baseline characteristics of the cohort of patients with essential thrombocythemia at registration.

	Total (N = 3649)		None (N = 187)		HC (N = 2305)		ANA (N = 481)		HC → ANA (N = 540)		ANA → HC (N = 116)	
Gender: female, n (%)	2238	(61)	126	(67)	1399	(61)	296	(62)	336	(62)	74	(64)
Age in years at registration, n (%)												
<40	249	(7)	34	(18)	51	(2)	102	(21)	44	(8)	15	(13)
40–59	931	(26)	59	(32)	382	(17)	240	(50)	192	(36)	52	(45)
60–79	1994	(55)	77	(41)	1487	(65)	124	(26)	253	(47)	46	(40)
80+	473	(13)	17	(9)	385	(17)	15	(3)	51	(9)	3	(3)
Treatment exposure at registration, n (%)												
None	187	(5)	187	(100)	0	(0)	0	(0)	0	(0)	0	(0)
HC	2305	(63)	0	(0)	2305	(100)	0	(0)	0	(0)	0	(0)
ANA	481	(13)	0	(0)	0	(0)	481	(100)	0	(0)	0	(0)
HC and then ANA	540	(15)	0	(0)	0	(0)	0	(0)	540	(100)	0	(0)
ANA and then HC	116	(3)	0	(0)	0	(0)	0	(0)	0	(0)	116	(100)
Had received both drugs, dates missing[a]	18	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Years between ET diagnosis[b] and registration, n (%)												
<1	744	(23)	14	(9)	571	(28)	108	(26)	38	(9)	8	(8)
1–2	406	(13)	20	(12)	285	(14)	47	(11)	43	(10)	9	(9)
3–4	882	(27)	51	(31)	548	(27)	123	(29)	116	(26)	37	(36)
5–9	767	(24)	54	(33)	432	(21)	102	(24)	140	(31)	39	(38)
10+	413	(13)	25	(15)	229	(11)	41	(10)	108	(24)	9	(9)

Abbreviations: ANA = anagrelide, ET = essential thrombocythemia, HC = hydroxycarbamide.

[a] Treatment exposure at registration could not be assessed for n = 18 subjects since date of first treatment with hydroxycarbamide/anagrelide was not available.

[b] Date of diagnosis could not be ascertained for n = 435 subjects.

Table 2

Total number of observed events in the study.

Acute myeloid leukemia	67
Myelodysplastic syndrome[a]	19
Skin cancer, including six malignant melanoma	35
Digestive organs	29
Respiratory organs	28
Male genital organs	21
Breast	18
Mesothelial and soft tissues	10
Urinary tract	10
Female genital organs	6
Eye, brain and central nervous system	5
Thyroid and other endocrine glands	5
Other sites	7
Chronic myeloid leukaemia	1
Patients with more than one cancer diagnosed	22
Total number of cancer diagnoses	261

[a] 3 patients had myelodysplastic syndrome first and then acute myeloid leukemia

Table 3

Standardized incidence ratios with 95% confidence intervals. A minimum of 180 days on drug required to be classified as exposed.

	Observed	Expected	Person-years	SIR	95% CI
Acute myeloid leukemia (C92.0)[a]					
ET without HC/ANA	0	0.03	331	0.00	(0.00–139)
ET with HC	39	0.98	8970	39.7	(28.3–54.3)
ET with ANA	0	0.08	1905	0.00	(0.00–45.7)
ET with HC and then ANA	20	0.22	2934	91.5	(55.9–141)
ET with ANA and then HC	3	0.04	802	68.5	(13.8–200)
Skin cancer (C43-C44)					
ET without HC/ANA	0	0.66	331	0.00	(0.00–5.64)
ET with HC	28	24.3	8967	1.15	(0.77–1.67)
ET with ANA	1	2.21	1905	0.45	(0.01–2.52)
ET with HC and then ANA	5	5.38	2941	0.93	(0.30–2.17)
ET with ANA and then HC	1	1.05	802	0.95	(0.01–5.30)
Skin cancer, other (C44)					
ET without HC/ANA	0	0.56	331	0.00	(0.00–6.61)
ET with HC	24	21.2	8968	1.13	(0.72–1.68)
ET with ANA	1	1.76	1905	0.57	(0.01–3.16)
ET with HC and then ANA	4	4.51	2941	0.89	(0.24–2.27)
ET with ANA and then HC	0	0.83	802	0.00	(0.00–4.47)
All cancers (C00-C96)					
ET without HC/ANA	0	4.64	331	0.00	(0.00–0.80)
ET with HC	159	166	8937	0.96	(0.81–1.12)
ET with ANA	8	15.4	1899	0.52	(0.22–1.02)
ET with HC and then ANA	53	39.1	2906	1.36	(1.02–1.77)
ET with ANA and then HC	7	8.31	795	0.84	(0.34–1.74)

Abbreviations: ANA = anagrelide, CI = confidence interval, ET = essential thrombocythemia, HC = hydroxycarbamide, SIR = standardized incidence ratio.

[a] Five patients with acute myeloid leukaemia with exposure to both HC and ANA were not included in the analysis, because there is uncertainty about which drug was given first.

Table 4

Risk ratios of standardized incidence ratios with bootstrapped 95% confidence intervals for the risk of acute myeloid leukaemia in patients changing exposure.

	HC→ANA versus HC		ANA→HC versus HC	
Minimal exposure time	Risk ratio	95% CI	Risk ratio	95% CI
180 days	2.30	(1.39–3.32)	1.72	(0.72–3.01)
One day	2.52	(1.59–3.63)	1.70	(0.72–3.02)

Abbreviations: ANA = anagrelide, CI = confidence interval, HC = hydroxycarbamide
Patients switching from HC to ANA and vice versa were assessed. The reference group was patients on HC only. Two analyses are shown: one with the restriction of 180 days on a drug is required to be classified as exposed, one without this restriction.